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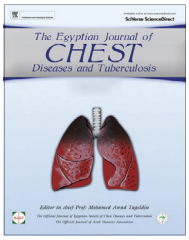

ORIGINAL ARTICLE

Evaluation of pulmonary fungal diseases in patients with fungal rhino-sinusitis

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KEYWORDS

Evaluation;
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Abstract *Setting:* Little is known on the concomitant occurrence of pulmonary fungal diseases in patients with fungal rhino-sinusitis.

Objective: To evaluate presence of pulmonary fungal diseases in patients with fungal rhino-sinusitis.

Patients and methods: A prospective study was done for 44 patients who fulfilled inclusion criteria (sinus CT, and histopathological examination). All patients were assessed for pulmonary symptoms, chest X-ray, CT scan, routine lab study, and broncho-alveolar lavage. Microscopic examination of fungal hyphae, fungal culture, skin prick tests, total and specific IgE was done to all cases.

Results: The mean age of patients was 32.5 ± 13.2. Fungal sinusitis was categorized into allergic FS 24 (54.5%) 6 of them (25%) were asthmatic, fungus ball 16 (36.4%) four (25%) were asthmatic, acute fulminant FS 3 cases (6.8%) one (33%) was asthmatic and chronic invasive sinusitis 1 (2.3%) not asthmatic. Eleven cases (25%) had pulmonary symptoms mainly cough and wheeze, malaise 7 cases (16%), dyspnea and fever 6 cases (14%), weight loss 3 cases (7%) and expectoration of golden brown cast in 2 cases (5%). Six patients (14%) had radiological involvement. Three cases (6%) in allergic FS group had the diagnostic criteria for sino-bronchial allergic mycosis (SAM). One patient

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was in acute stage I, second was in stage III corticosteroid dependant state, and third was in stage 1V of exacerbation with high total, specific IgE for *Aspergillus fumigatus*.

Conclusion: Universal screening for pulmonary fungal infection especially in patients with fungal rhino sinusitis is highly recommended to treat it early, decrease morbidity and mortality of the diseases.

Introduction

The relationship between upper airways and lower airways has been studied for about 50 years. In this concept, upper and lower airway diseases are considered as two manifestation of one pathologic process [1]. Sinopulmonary syndromes result from diseases that affect both the paranasal sinuses and the lower respiratory tract. Venarske and deShazo, in 2002 [2], coined the term 'sinobronchial allergic mycosis' (the SAM syndrome) to describe the expression of fungal hypersensitivity in both upper and lower airways, this was on the basis of five patients reported for their rare presentations.

The three main clinical categories of aspergillus fungus are allergic aspergillosis, invasive disease and saprophytic colonization [3]. Fungal rhinosinusitis has been described for many years, initially in immunocompromised patients, but since the development of nasal endoscopy, several new cases have been reported in immunocompetent patients [4]. Millar and colleagues [5] described the first case of allergic aspergillosis of the maxillary sinuses. Subsequently known as allergic aspergillus sinusitis (AAS), its clinico-pathological similarity to ABPA was recognized [6].

Sher and Schwartz in 1988 [7] published the first report of a case of AAS with concurrent ABPA. Several such cases have since been reported [8–10]. Fungal rhinosinusitis has been separated into invasive and noninvasive forms. In cases of acute fulminant invasive fungal sinusitis, patients are usually immunocompromised and frequently the prognosis is poor [11]. Allergic bronchopulmonary aspergillosis (ABPA), predominantly occurs in asthmatics. Aspergilloma is a fungal ball that appears in a pre-existing cavity. These patients frequently experience wheezing dyspnea with signs of airway obstruction [12]. Cavities are not infrequent in ABPA, with formation of an aspergilloma might be accelerated by therapy with corticosteroids [13].

The prevalence of concurrent ABPA and AAS is not known. There have been very few studies which have evaluated the presence of AAS in patients of ABPA and vice versa [14]. There is little knowledge on the concomitant occurrence of pulmonary fungal diseases in patients with fungal rhinosinusitis.

Aim of the study

This study aimed to investigate the presence of pulmonary fungal diseases in patients with fungal rhino-sinusitis, and identify which category of fungal affection (allergy or fungal infections) in both upper and lower airways more liable to occur simultaneously.

Material and methods

A prospective study was started in March 2011; Patients with clinical and documental diagnosis of fungal rhino sinusitis who attended ENT department at Sohag University hospital were invited to participate. The study was approved from the ethics committee of our faculty of medicine. Procedures were explained and obtained written informed consent from the patients. Data obtained from the enrolled patients included information about demographics, detailed medical history.

Criteria for inclusion and exclusion

Sixty patients with suspicious of fungal rhinosinusitis (FRS) were assessed and evaluated using paranasal sinuses' endoscopic surgical procedure with complete removal of fungal contents from involved sinuses. Out of 60 patients 44 patients were diagnosed FRS, based on clinical, radiological sinuses CT scan, direct mycological and/or fungal culture and/or histopathologic analysis. These patients who met the criteria of fungal rhino-sinusitis were evaluated for detection of pulmonary fungal diseases. Sixteen patients were excluded from the study because four did not agree to participate in the study or sign the informed consent term, and twelve patients did not meet the above mentioned criteria.

All patients were subjected to Chest plain X-ray and CT scan of which CT scans nose and paranasal sinuses.

Laboratory investigations

Hematological examination includes complete blood picture, differential white blood cells especially absolute count of eosinophil, and erythrocyte sedimentation rate. Blood chemistry includes blood sugar examination and liver, renal function tests.

Bacteriological examination

The first early morning sample should be collected into a sterile container. Culture and sensitivity test for non specific microorganism of the available samples repeated sputum smear and culture for *Mycobacterium tuberculosis* were performed.

Pulmonary function tests

All subjects underwent complete pulmonary function testing using (Medizintechnik mit System, JAEGER, TOENNIES, Hoechberg/Germany) for confirmation of the diagnosis of bronchial asthma and assessment of its severity. Pre- and post-bronchodilator tests were performed. Lung volumes and flows were measured and the normal values were considered according to the European Respiratory Society references [15].

Immunological studies by enzyme-linked immunosorbent assay (ELISA)

The serum specimens were stored at −20 °C until the time of ELISA test performance [16]. Total serum immunoglobulin E (LgE): Normal values are up to 200 IU/ml. *Aspergillus fumigatus* (AF specific IgE): The test was considered to be positive if the result ⩾0.35 IU/mL. *A. fumigatus* (AF specific IgG): >12 U/ml was considered positive.

Skin prick test

The used antigens were *A. fumigatus*, *Aspergillus flavus* and *Aspergillus niger*. Histamine phosphate (5 mg/ml, as a positive control) and negative control solutions were also used (the antigens and positive and negative controls were supplied by the Allergopharma Joachim Ganzer KG company) [17].

Specimens' collection

The samples were sent for direct microscopic study, histopathology in formalin solution and culture specimen was sent in normal saline sterile bottles.

Bronchoalveolar lavage (BAL) samples

A sterilized fiberoptic bronchoscope was carried out in a standard fashion with diazepam and atropine sulfate for premedication; this followed by local anesthesia with lignocaine 10% for the pharynx and lignocaine 2% for tracheobronchial use. Fiberoptic bronchoscope was introduced by the nasal or buccal route with the patient in a semi seated position or sometimes in the supine position. Thorough inspection of the tracheobronchial tree was completed. Lavage is usually performed in the right middle or upper lobe or in the lingual. 100–300 mL of saline is instilled in aliquots of 20–60 mL, the fluid is immediately aspirated at low pressure.

Direct microscopic examination

The specimen for fungal staining is mixed with 10% or 20% potassium hydroxide (KOH) and examined.

Histopathology

Histopathologic techniques are more time-consuming but they provide the only method of determining whether a fungus is invading into host tissue by using hematoxylin and eosin (H&E) stain.

Gomori methenamine silver (GMS) stain

It was used in all cases as it is more superior to H&E stains.

Fungal culture

All samples were placed into centrifuge tubes and sent to the mycology laboratory within 24 h. Selection and inoculation of culture media: Using non selective Sabouraud's dextrose agar (2%) [18].

Diagnostic criteria and categorization of fungal rhino-sinusitis:

1. *Allergic fungal sinusitis:* Five criteria for the diagnosis of AFS: [19] nasal polyposis; allergic mucin; CT scan findings consistent with chronic rhinosinusitis; Histological presence of fungal hyphae, positive fungal culture; and type I hypersensitivity (atopy) diagnosed by history, positive skin test, or serology.
2. *Fungal ball:* Patients with symptoms of unilateral or bilateral nasal obstruction, pressure feelings and nasal discharge with the detection of a mass of mycelia embedded in mucus within the paranasal sinuses without mucosal invasion on histopathology [11].
3. *Acute fulminant fungal sinusitis:* It is described by a time course of <4 weeks caused by rapid spread of fungi from the nasal mucosa and sinuses into the orbit, vessels, and brain parenchyma. "Prognosis is poor," This is characterized by evidence of angio-invasion by fungal hyphae [20].
4. *Chronic invasive fungal sinusitis:* The disease typically has a time course of >12 weeks characterized by mass of hyphae, occasional presence of vascular invasion, and sparse inflammatory reaction in association with involvement of local structures. The mass of hyphae may extend into the brain [21].

Statistical analysis

All statistical analyses were performed using the SPSS statistical package (version 11 for Windows, SPSS; Chicago, Ill., USA). The association and relationship between 2 quantitative variables were evaluated with Chi-square test. The results were expressed as the means and standard deviation for quantitative variables and as frequencies for categorical findings. To compare the means of 2 independent groups, Student's *t* test was used. The level of statistical significance was taken as p value < 0.05.

Results

Total of forty four patients was enrolled in the study. The mean age of patients was 32.5 ± 13.2 years ranging from 11 to 60 years with 21 (48%) male and 23 (52.3%) female. The patients diagnosed as having paranasal sinus mycoses were categorized into four disease groups. Allergic FS was noted in 24 (54.5%), fungal ball in 16 (36.4%), acute fulminant FS in 3 (6.8%) and chronic invasive FS in 1 (2.3%) as shown in (Table 1).

Out of 24 patients of AFS 13 were males and 11 were females with the mean age of 26.97 years. None of the patients were immune-compromised. Among the AFS group 6 (25%) were asthmatic. Two cases (8%) had aspirin hypersensitivity,

Table 1 Distribution of different patients' groups according to paranasal sinus mycosis.

	Category of fungal sinusitis	No. (%)
Group	Allergic fungal sinusitis	24 (54.5)
Group	Fungal ball	16 (36.4)
Group	Acute fulminant FS	3 (6.8)
GroupV	Chronic invasive FS	1 (2.3)
Total		44 (100)

one of them fulfilled the criteria of Samter's triad, which is, nasal polyposis, asthma, and aspirin intolerance. Sixteen cases (66.7%) had elevated total serum IgE. Three cases exceeded 1000 IU/mL. Mean serum levels of Aspergillus specific IgE were 0.3942 ± .2330 and elevated in 14 (58.3%) cases of AFS. Mean serum levels of Aspergillus specific IgG were 11.24 ± 7.2 and was elevated in 11(45.8%) cases of AFS. Only skin test reactivity and total serum immunoglobulin E showed a significant difference among the AFS and non-AFS groups regarding atopy ($P < 0.05$) (Table 2).

Thirteen patients had positive fungal culture. Aspergillus was recovered on culture in 13(54.2%) cases and no fungal growth was reported in 11 (45.8%) cases. *A. fumigatus* was a single fungus isolated in 10 cases.

A. fumigatus grew combined with *A. niger* in one case. Three Aspergillus species (*A. fumigatus*, *A. flavus* and *A. niger*) were isolated in one case. *Candida albican* was also grown in addition to *A. niger* in one case in the allergic fungal sinusitis group (Figs. 1–3).

Fungus ball (16 cases, 36.4%)

Out of 16 patients 10 (62.5%) were females and 6 (37.5%) were males with the mean age of 41.68 years. All patients were immune-competent. Nine of the patients (56.25%) have been subjected to homolateral endodontic surgery in the past. Four (25%) patients were asthmatic, two cases (12.5%) had aspirin hypersensitivity, 3 (18.5%) had elevated total IgE level. Only total IgE and skin test reactivity showed a significant difference among the AFS and non-AFS groups regarding atopy ($P < 0.05$). There were statistically significant differences between AFS and fungus ball groups as regards total IgE, specific IgE and IgG for aspergillus. Tables 3 and 4.

Acute fulminant FS (3 cases, 6.8%)

Three patients were acute fulminant FS in our study, including two males and one female. Their ages were 19, 22 and 34. Two of the three patients died. All had an underlying diseases associated with immune compromised status. Case no. 1 is a 19 year old female patient, presented with fever, ulceration of palatal mucosa, facial anesthesia and mental status changes. She had neutropenia and renal failure. Case no. 2 is a 22 year old male patient, presented with fever, severe headache and ophthalmologic complaints, including proptosis, periorbital pain and decreased visual acuity. He had neutropenia. Case no. 3 is a 34 year old male patient, presented with fever and localizing symptoms of rhinosinusitis. He had uncontrolled diabetes. CT scan revealed evidence of invasion. Culture in these patients revealed Mucormycosis in two cases (Fig. 4) and Aspergillus species in the third case.

All cases had negative skin test reactivity to *Aspergillus* antigen. Lab investigations showed increased level of total serum IgE in one case. Serum levels of Aspergillus specific IgE and Aspergillus specific IgG were negative.

Chronic invasive FS (1 case, 2.3%)

A 42 year old immunocompetent female presented with 8 month history of chronic rhinosinusitis; a month history of painless proptosis of the left eye. She denied diplopia, headaches or change in vision. CT scan of the paranasal sinuses revealed a mass involving the left orbit with invasion of the medial wall of the maxillary sinus, lamina papyrecea and the nasal septum. Mucosal invasion by fungus was also identified. Aspergillus culture was negative. Immunological tests were negative.

Presence of pulmonary fungal diseases in patients with fungal rhino-sinusitis

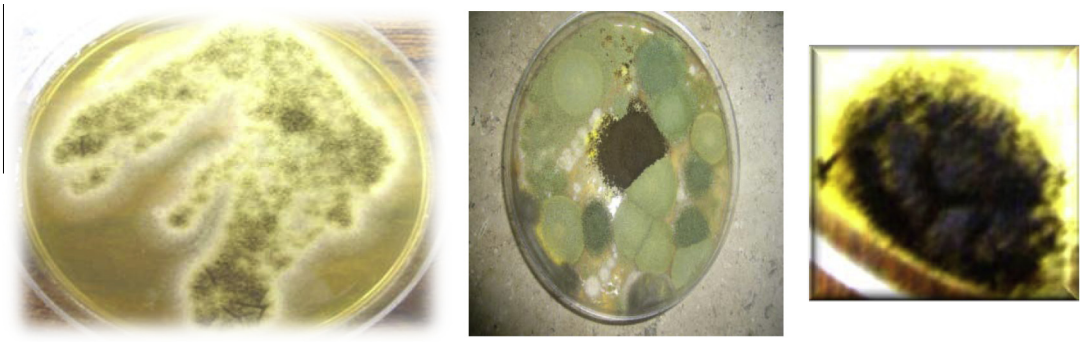
Eleven patients (25%) had pulmonary symptoms mainly cough, dyspnea, malaise, (Table 5) and all of them were asthmatics. Of these 11 patients, the preliminary radiography of the chest revealed pulmonary involvement in 6 patients (14%). After laboratory investigations including; histopathological examination, bacteriological examination (stain to exclude acid fast bacill, culture and sensitivity test for non specific micro-organism), fungal culture and immunological workup (skin test, total serum immunoglobulin E, *A. fumigatus* "AF IgE" and *A. fumigatus* "AF IgG") were performed. Confirmation of pulmonary fungal diseases was available in three patients (6.8%). All had positive family history of asthma and or rhinitis, hyphae, positive culture and positive GMS stain.

These three cases were found in allergic fungal sinusitis group and had the full diagnostic criteria of sinobronchial allergic mycosis (SAM). One of them had Allergic bronchopulmonary aspergellosis (ABPA) plus AFS and pulmonary fungus ball. Cough and expectoration were the predominant symptoms in all the three patients, also were observed to have wheezing and fever during exacerbation, while dyspnea and chest pain were reported by two cases. Passage of golden brown casts along with sputum was reported by two patients, while one patient had hemoptysis, who had an aspergilloma (Table 6).

The three patients who diagnosed as having Allergic (ABPA) can be subdivided according to the stage of Allergic

Table 2 Comparing atopic state among AFS and non-AFS groups in 44 FRS patients.

Variables	AFS (24 cases)		Non AFS (20cases)		*P* value
	No.	%	No.	%	
Asthmatic	6	(25%)	5	(25)	1.00
Aspirin hypersensitivity	2	(8.3%)	2	(10)	0.848
High total IgE	16	(66.7%)	4	(20)	0.003
Positive skin test	14	(58%)	3	(15)	0.003
Peripheral eosinophilia	10	(41%)	7	(35)	0.651



Figures 1–3 Three Aspergillus species (*Aspergillus fumigatus*, *Aspergillus flavus* and *Aspergillus niger*) growth on Sabouraud's agar.

Table 3 Atopic state among AFS and fungus ball groups.

Variables	AFS (24 cases)		Fungus ball (16 cases)		*P* value
	No.	%	No.	%	
Asthmatics	6	25	4	25	0.64
Aspirin sensitivity	2	8.3	2	12.5	0.52
High total IgE	16	66.7	3	18.5	0.003
Positive skin test	14	58	3	18.5	0.01
Eosinophilia	10	41.7	6	37.5	0.42

Table 4 Comparing both means of total serum IgE, serum levels of Aspergillus specific IgE and serum levels of Aspergillus specific IgG among the AFS and fungus ball groups.

Variables	Category of fungal sinusitis	Mean ± SD	*P* value
Total IgE	AFS 24 cases	521.96 ± 446.60	0.003
	Fungus ball 16 cases	136.94 ± 107.43	
Specific aspergillus IgE	AFS	0.39 ± .2330	0.001
	Fungus ball	0.18 ± 7.719E-02	
Specific aspergillus IgG	AFS	11.246 ± 7.297	0.002
	Fungus ball	6.475 ± 2.476	

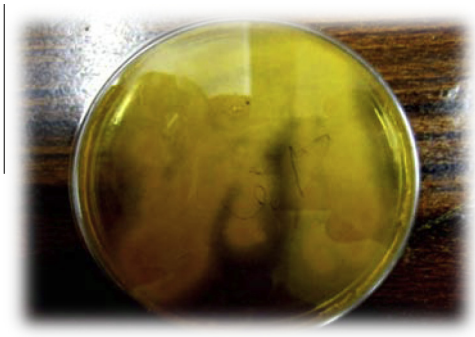


Figure 4 Mucor is a rapidly growing fungus which will fill a culture plate in a matter of a few days with a woolly growth resembling cotton candy. New growth is white in color but turns a greyish-brown with aging.

Table 5 Pulmonary manifestations in patients with fungal rhinosinusitis.

Variable	No.	(%)
Cough	11	(25.00)
Chest pain	2	(4.54)
Hemoptysis	1	(2.27)
Wheeze	11	(25.00)
Sputum production	8	(18.18)
Passage of golden brown casts	2	(4.54)
Dyspnea	6	(13.63)
Fever	6	(13.63)
Weight loss	3	(6.82)
Malaise	7	(15.91)

(ABPA) into: Patient No. 1 in the stage III (exacerbation stage) as the patient is known to have ABPA, asthmatic, radiological central bronchiectasis, the IgE level was markedly elevated (1034 IU/mL), *A. fumigatus* IgE was elevated (0.75 IU/mL), *A. fumigatus* IgG was elevated (19 U/mL), and with peripheral eosinophilia, Patient No. 2 in the stage IV (the corticosteroid-dependent stage) the patient was steroid-dependent with attempted to taper the steroid therapy, resulting in an obvious worsening of symptoms and the radiological central bronchiectasis. The serum IgE level was elevated (950 IU/

Table 6 Clinical pulmonary profile of three patients with concomitant ABPA and AFS.

Case number	1	2	3
Age/sex	26/M	30/M	40/F
Chest manifestations			
Duration of illness (yr)	4	1	2
Cough	+	+	+
Expectoration	+	+	+
Plugs/casts	+	–	+
Wheeze	+	+	+
Dyspnea	+	–	+
Chest pain	+	–	+
Hemoptysis	+	–	–
Fever	+	+	+
Weight loss	+	–	–
Malaise	+	–	+
Family history			
Asthma	Father	–	Sister
Rhinitis	Father	Mother	–
Past treatment: Antibiotics	+	+	+
Decongestants	+	+	+
Antituberculous therapy	+	–	–
Steroid therapy	+	+	+
Asprin intolerance	+	–	–

Table 7 Laboratory data of three patients with concomitant ABPA and AFS.

Case Number	1	2	3
BAL/sputum specimen AFB smear	+	–	–
Eosinophilic infiltration	+	+	+
Fungal culture	+	+	–
Fungal hyphea: H&E stain	+	+	–
GMS stain	+	+	+
Spirometry: FVC (%)	67.00	85.00	71.00
FEV1(%)	59.00	81.00	54.00
FEV1/ FVC(%)	88.05	95.30	76.05
Skin test	+	+	+
Total IgE (IU/mL)	1034	950	1786
Aspergillus fumigatus IgE (IU/mL)	0.75	0.68	0.95
Aspergillus fumigatus IgG (U/mL)	19.0	17.0	34.0

mL), *A. fumigatus* IgE was elevated (.68 IU/mL), *A. fumigatus* IgG was elevated (17 U/mL), and with peripheral eosinophilia, Patient No. 3 in the Stage1 (acute stage), is asthmatic, radiological pulmonary infiltrates and central bronchiectasis, the IgE level was markedly elevated(1786 IU/mL), *A. fumigatus* IgE was elevated (0.95 IU/mL), *A. fumigatus* IgG was elevated (34.0 U/mL), and with peripheral eosinophilia,

Plain chest X-ray revealed central bronchiectasis (CB) with normal peripheral bronchi, a diagnostic feature of ABPA, and transient pulmonary infiltrates in all the three patients. Computed tomography confirmed the features of chest X-ray findings. The patient who had an aspergilloma concomitant with Allergic (ABPA) revealed loculated hydropnemothorax in the right lung. Solitary well defined mycelial mass occupying a cavity in the left middle lobe. The cyst wall is smooth and thin.

Pulmonary histopathological examination

Cytological examination of the material obtained with bronchial brushing disclosed numerous eosinophils, Charcot–Leyden crystals and fungal structures morphologically corresponded to *A. fumigatus* in all cases. About lung function test; the three cases were asthmatic and had a forced expiratory volume in 1 second (FEV1) of less than 80% of normal. One of them had ABPA with normal lung volumes and flow rates, even in the presence of bronchiectasis. PFT in the other two patients showed reduction in total lung capacity, forced vital capacity (FVC), forced expiratory volume in the first second (FEV1). Arterial blood gas analysis showed only mild hypoxemia (pO_2 9 kPa). Positive hypersensitivity reactions were observed in all three patients. Total IgE was raised in all three patients. *A. fumigatus* IgE/IgG was positive by ELISA in three patients. Peripheral eosinophilia was observed also in the three patients as shown in (Table 7).

There is insignificant difference between AFRS group to non allergic fungus group as regards the incidence of pulmonary affection, P value = 0.153 but there is also a significant positive strong correlation between total serum IgE and *A. fumigatus* IgE.

Discussion

In spite of similar histopathological features between the allergic mucin of AAS and the mucous plugs of ABPA, concomitant occurrence of ABPA and AAS appears to be rarely reported and there have been very few studies consisting of case reports which have evaluated the presence of AAS in patients of ABPA and vice versa [14,22]. Forty four patients were categorized into four pathologic groups: (1) allergic fungal sinusitis in 24 cases (54.5%) (2) mycetoma/fungus ball in 16 cases (36.4%); (3) acute fulminant fungal sinusitis in 3 cases (6.8%); and (4) chronic invasive fungal sinusitis in 1 case (2.3%). These results matched with Montone et al., 2012 [23] who reported 45% AFRS, 40% FB, 2% combined AFRS and FB and 12.5% were invasive 11% AIFRS and 1.2% CIFRS. M.T. Hedayati et al., 2010 [24] reported higher incidence of AFRS (80%), followed by FB (20%) as well as Granville et al., 2004 [25] who reported that allergic FS is the most frequent and accounts for 72% of cases, followed by chronic non-invasive FS (23%), whereas both chronic invasive and acute fulminant FS are quite rare.

Studying of 44 patients with fungal rhinosinusitis proved the presence of concomitant ABPA in three patients of the 24 patients who had allergic fungal sinusitis. Association of ABPA, AFS and aspergilloma in the same patient was found only in one case. This confirms that the pathogenesis of ABPA and AFS is similar to each other, and differs from any other fungal rhinosinusitis category. In addition patients with AFS are at risk of developing ABPA and vice versa. This is consistent with multiple studies [2,9,26,27]. Venarske and deShazo in 2002 have termed this process the SAM syndrome, an acronym for sinobronchial allergic mycosis [2].

The affected patients were 2 men and a woman, age range of 26–40 years. All had a history of asthma and chronic sinusitis and family history of asthma and/or rhinitis. These findings are consistent with Venarske and Shah [2,27]. Past history of

receiving anti-tuberculous treatment was found in one patient, who had an aspergilloma, while Shah et al., 2001 [27] reported five cases. All the three patients had history of passage of nasal golden brown casts and two of them were presented by passage of golden brown casts along with sputum beside the dyspnea and chest pain. Hemoptysis was the alarming presentation of only one patient, who had an aspergilloma. Attapattu in 1991 [28] reported that passage of golden brown casts along with sputum is one of the minor criteria for the diagnosis of ABPA.

In this study patients with SAM are atopic individuals; all the 3 cases had asthma, peripheral eosinophilia, positive skin test reactions and high levels of total IgE. Only one gave history of aspirin intolerance. Patients with SAM showed high levels of total IgE, two of them exceeded 1000 IU/mL and the other patient's level was 950 IU/mL, and this stressed that AFS patients with high levels of total IgE could be at risk for the development of ABPM. These findings are also in agreement with Venarske and deShazo in 2002 [2]. Shah and Sircar in 1991 [29] stated that both AFS and ABPA have the same mechanism, which is likely that the release of antigenic material from Aspergillus sets into motion a chain of immunologic reactions leading to the development of both AFS and ABPA.

Chest radiographic findings revealed central bronchiectasis in the three patients; besides hydropnemothorax in the right lung. Solitary well defined mycelial mass occupying a cavity in the left middle lobe of the patient who has association of ABPA, AFS and aspergilloma. Venarske and deShazo in 2002 and Shah et al., 2001 [2,27] reported that all had radiographic evidence of central bronchiectasis which is essential pathognomic feature of ABPA as documented by Scadding in 1967 [30].

Consequently, ABPA patients with nasal CT revealing double dense lesions should be investigated carefully to exclude AFS. As well, AFS patients with central bronchiectasis detected by chest radiography are considered as APBA until investigated. The histopathologic findings of both nasal allergic mucin and bronchoalveolar lavage of the three patients showed the same features, eosinophilic mucin contained Charcot–Leyden crystals and fungal hyphae were noted within the ''allergic mucin'', support that these are similar hypersensitivity reactions to fungal elements occurring at different locations in the same airway and the pathogenesis of these diseases is similar.

In this study culture of bronchial samples Aspergillus species in all affected cases and repeated sputum stains and culture were negative for *M. tuberculosis* in all cases. This is in agreement with Shah et al., 2001 [27]. In the current study pulmonary function test revealed obstructive ventilator defect in two of the three patients, while Shah et al., 2001 [27] reported obstructive ventilator defect in all his studied seven patients. This result is not pathognomic for ABPM, but when AFS patient presented with obstructive ventilator defect; the physician should be alert to the possibility of coexistent ABPA or just asthma. In the current study, one patient presented with an association of ABPA, AFS and aspergilloma, the patient was asthmatic, had a history of corticosteroids therapy and past history of receiving anti-tuberculous treatment. It is not known if aspergilloma preceded ABPA or ABPA was developed earlier. This was in agreement with Sharma et al [13].

Among the AFS patients, 6 (25%) were asthmatic, only 2 patients (8%) had a history of aspirin intolerance; one of them fulfilled the criteria of Samter's triad. Comparison between AFS group and non-AFS group revealed there is statistically insignificant difference among these 2 groups in relation to asthma, aspirin sensitivity, and peripheral blood eosinophilia. The significant differences were founded in the positive skin test reactivity and elevated total IgE, while Bee et al., in 2005 [31] showed statistically insignificant difference in relation to asthma, aspirin sensitivity, and total IgE. The only significant issue was the positive skin test reaction; he revealed also two AFS patients were identified as having Samter's triad. Cody et al., in 1994 [32] described a higher incidence of aspirin sensitivity in AFS patients of 27%.

Conclusion

Patients with asthma and/or rhinosinusitis along with sensitization to aspergillus antigens are at an increased risk of developing ABPA and/or AAS. ABPA must be excluded in all patients with AAS and vice versa. Patients who presented with passage of nasal and sputum plugs should alert the physician to the possibility of coexistent ABPA and AAS. Presence of hemoptysis in ABPA patient considers an alarming manifestation for developing aspergilloma.

AFS patient presented with highly elevated total IgE should raise the suspicion of having ABPA. Presence of double dense lesions in the nasal CT and central bronchiectasis in the chest radiography of the same patient should strengthen the suspicion of having concomitant ABPA and AFS in this patient.

There is evidence that only AFS category has similar immunological pathogenesis to ABPA and not any other category of fungal rhinosinusitis as these immunological similarities between ABPM and AFS are not present in the immunological laboratory findings of FB, AIFS and CIFS.

Universal screening for pulmonary fungal infection especially in patients with fungal rhino sinusitis is highly recommended. There is an urgent need to treat it early to decrease morbidity, mortality and alter the course of the diseases.

Conflict of interest

None declared.

References

[1] M. Tosca, A. Riccio, G. Marseglia, et al, Nasal endoscopy in asthmatic children: assessment of rhinosinusitis and adenoiditis incidence, correlations with cytology and microbiology, Clin. Exp. Allergy 31 (2001) 609–615.
[2] D. Venarske, R. deShazo, Sinobronchial allergic mycosis, Chest 121 (2002) 1670–1676.
[3] A. Shah, Allergic bronchopulmonary aspergillosis, Indian J. Chest Dis. Allied Sci. 40 (1998) 41–54.
[4] B. Ferguson, Mucormycosis of the nose and paranasal sinuses, Otolaryngol. Clin. North Am. 33 (2000) 349–365.
[5] J. Millar, A. Johnston, D. Lamb, Allergic aspergillosis of the maxillary sinuses, Thorax 36 (1981) 710.
[6] A. Katzenstein, S. Sale, P. Greenberger, Allergic aspergillus sinusitis: a newly recognized form of sinusitis, J. Allergy Clin. Immunol. 72 (1983) 89–93.
[7] T. Sher, H. Schwartz, Allergic aspergillus sinusitis with concurrent allergic bronchopulmonary Aspergillus: report of a case, J. Allergy Clin. Immunol. 81 (1988) 844–846.

[8] A. Shah, Z. Khan, S. Chaturvedi, et al, Concomitant allergic aspergillus sinusitis and allergic bronchopulmonary aspergillosis associated with familial occurrence of allergic bronchopulmonary aspergillosis, Ann Allergy 64 (1990) 507–512.
[9] A. Shah, C. Panjabi, Contemporaneous occurrence of allergic bronchopulmonary aspergillosis, allergic aspergillus sinusitis and aspergilloma, Ann. Allergy Asthma Immunol. 96 (2006) 874–878.
[10] G. Erwin, J. Fitzgerald, Allergic bronchopulmonary aspergillosis and allergic fungal sinusitis successfully treated with voriconazole, J. Asthma 44 (2007) 891–895.
[11] R. De Shazo, M. O'Brien, K. Chapin, et al, A new classification and diagnostic criteria for invasive fungal sinusitis, Arch. Otolaryngol. Head Neck Surg. 123 (1997) 1181–1188.
[12] A. Shah, Z.U. Khan, S. Chaturvedi, et al, Allergic bronchopulmonary aspergillosis with coexistent aspergilloma. A long term follow up, J. Asthma 26 (1989) 109–115.
[13] P. Sharma, A. Agarwal, A. Shah, Formation of an aspergilloma in a patient with allergic bronchopulmonary aspergillosis on corticosteroid therapy, Indian J. Chest Dis. Allied Sci. 40 (1998) 269–273.
[14] C. Panjabi, A. Shah, Allergic aspergillus sinusitis and its association with allergic bronchopulmonary aspergillosis, Asia Pac. Allergy 1 (2011) 130–137.
[15] P. Qanjer, G. Tammeling, J. Cotes, et al, Lung volumes, and forced ventilatory flows, Eur. Respir. J. 6 (Suppl. 16) (1993) 15–40.
[16] National Committee for Clinical Laboratory StandardsProcedures for the Collection of Blood Specimens by Venipuncture, third ed., NCCLS, 1991, Doc H3–A3.
[17] A. Zawodniak, M. Kupczyk, P. Górski, et al, Comparison of standard and modified SPT method, Allergy 58 (2003) 257–259.
[18] P. Murray, ASM Poket Guide to Clinical Microbiology, ASM Press, Washington, D.C., 1996.
[19] J. Bent, F. Kuhn, Diagnosis of allergic fungal sinusitis, Otolaryngol. Head Neck Surg. 111 (1994) 580–588.
[20] M. Ghadiali, N. Deckard, U. Farooq, et al, Frozensection biopsy analysis for acute invasive fungal rhinosinusitis, Otolaryngol. Head Neck Surg. 136 (5) (2007) 714–719.
[21] R. Washburn, D. Kennedy, M. Begley, et al, Chronic fungal sinusitis in apparently normal hosts, Medicine (Baltim) 67 (1988) 231–247.
[22] A. Shah, Asthma and aspergillus, Indian J. Chest Dis. Allied Sci. 46 (2004) 167–170.
[23] T. Montone, A. Livolsi, Michael D. Feldman, et al, Fungal Rhinosinusitis: A Retrospective Microbiologic and Pathologic Review of 400 Patients at a Single University Medical Center, Int. J. Otolaryngol. (2012).
[24] M. Hedayati, M. Bahoosh, A. Kasiri, et al, Prevalence of fungal rhinosinusitis among patients with chronic rhinosinusitis from Iran, J. Mycol. Méd. 20 (2010) 298–303.
[25] L. Granville, M. Chirala, P. Cernoch, Fungal sinusitis: histologic spectrum and correlation with culture, Hum. Pathol. 35 (4) (2004) 474–481.
[26] M. Schubert, D. Goetz, Evaluation and treatment of allergic fungal sinusitis: I Demographics and diagnosis, J. Allergy Clin. Immunol. 102 (3) (1998) 387–394.
[27] A. Shah, N. Panchal, A. Agarwal, Concomitant allergic bronchopulmonary aspergillosis and allergic aspergillus sinusitis: a review of an uncommon association, Clin. Exp. Allergy 31 (2001) 1896–1905.
[28] M. Attapattu, Allergic bronchopulmonary aspergillosis among asthmatics, Ceylon Med. J. 36 (1991) 45–51.
[29] A. Shah, M. Sircar, Sensitization to aspergillus antigens in perennial rhinitis, Asian Pac. J. Allergy Immunol. 9 (1991) 137–139.
[30] J. Scadding, The bronchi in allergic aspergillosis, Scand. J. Respir. Dis. 48 (1967) 372–377.
[31] G. Bee-See, S. Balwant, R. Isa, et al, Prevalence of allergic fungal sinusitis in refractory chronic rhinosinusitis in adult Malaysians, Otolaryngol. Head Neck Surg. 133 (2005) 27–31.
[32] D. Cody, H. Neel, J. Ferreiro, et al, Allergic fungal sinusitis: the Mayo Clinic experience, Laryngoscope 104 (1994) 1074–1079.